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Hyperinsulinism

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DEFINITION OF HYPERINSULINISM

For the purpose of this paper hyperinsulinism is defined as any abnormal state in which there is an excessive action of insulin. Hyperinsulinism may be due to an abnormally large amount of insulin acting in the presence of normal amounts of antagonistic factors (absolute hyperinsulinism) or to a normal amount of insulin acting in the presence of subnormal amounts of these factors (relative hyperinsulinism). The state may arise from the administration of exogenous insulin or the production of endogenous insulin. It follows from this definition that a condition, in which there is an abnormally large amount of insulin and insulin antagonists available to the tissues with a normal action of insulin, is not considered to be hyperinsulinism.

This definition of hyperinsulinism in terms of excess insulin action rather than excess insulin availability has been chosen deliberately (Gorsuch and Rynearson, 1944; Marks and Rose, 1965) in spite of the fact that it renders recognition of the state much more difficult. This is because, in considering the insulin status of the individual from the clinical point of view, one's primary concern should be with the maintenance of normal insulin action. As a result of this concern one is of course interested in the insulin output and the identification of states of high or low insulin secretion rate. However, high output states in themselves theoretically need not be associated with hyperinsulinism as I have defined it. Another consequence of this definition is that it is theoretically possible to have hyperinsulinism of an individual tissue without there being general hyperinsulinism. There is no reason to believe that antagonists of insulin action on muscle will also antagonize its action on adipose tissue or liver; in fact the evidence suggests the converse (Karl, Voyles, and Recant, 1968). Equally there is no reason to believe that the dose-response relationship of insulin acting on liver, muscle, and adipose tissue will be the same. For example, maximal stimulation of the glucose uptake of rat epididymal fat pad by insulin is often observed at concentrations of 100 to 200 μUnits/ml whereas that of rat hemidiaphragm occurs at about 10 mUnits/ml. Furthermore for a single tissue the dose-response relationship of the effects of insulin on different aspects of metabolism may differ markedly. Thus rat and human isolated fat cells are extremely sensitive to the antilipolytic effect of insulin, and concentrations of insulin as low as 0·1 μUnits/ml have a marked inhibitory effect on lipolysis (Fain, Kovacev, and Scow, 1966) but relatively little stimulatory effect on glucose uptake. However, at levels of 1,000 μUnits/ml or more insulin may actually increase lipolysis whereas it does not inhibit glucose uptake at these concentrations (Hales, Chalmers, Perry, and Wade, 1968). Conversely insulin increases amino-acid incorporation into fat-cell protein throughout the range 10 to 800 μUnits/ml (Miller and Beigelman, 1967). These findings suggest the possibility that hyperinsulinism in the fasting state may produce a different pattern of metabolic abnormalities from that produced by hyperinsulinism in the fed state.

This approach, therefore, while it emphasizes the complexity of the concept of hyperinsulinism and (as will be apparent later) the scarcity of really relevant information, also indicates the problems that require investigation and the ways in which they can be tackled.

RECOGNITION OF HYPERINSULINISM

The proof of excessive action of insulin on a tissue at a particular time involves the measurement of the rates of all the reactions affected by insulin, and the demonstration that these rates are excessive and that they can be rendered normal by reducing the amount of insulin available to the tissue. A less certain indication of hyperinsulinism is provided by the demonstration that the administration of extra insulin results in a relatively poor insulin effect, but this could result from excessive insulin antagonism. The difficulties in approaching this problem lie in the technical difficulty of studying human tissue in its living state, in the sheer number of effects of insulin already described, and in the near certainty

that there remain still further effects as yet undescribed.

One of the crudest but simplest ways of measuring tissue rates of reactions which are affected by insulin is to estimate the concentrations of substances in the blood whose metabolism is insulin-dependent. It is salutary to remember that most such investigations have been limited to the determination of blood glucose concentration. There are a number of other parameters which might be measured with advantage in certain situations, including plasma potassium, phosphate, non-esterified fatty acids, glycerol, triglycerides, amino-acids, and other hormones such as growth hormone. Again it must be recognized that there are probably important effects of insulin as yet undefined. In this respect the effect of insulin on the release of other hormones is likely to be very important. These estimations do not give a good indication of the site of excess insulin action: for example, a low blood glucose concentration could result from an excessive reduction of liver glucose output or excessive stimulation of glucose uptake peripherally or both. An improvement on this technique, therefore, is the use of labelled glucose to study the relative rate of liver glucose output (see review by Cahill and Owen, 1968). Also the recently introduced technique of using a regulated glucose infusion can supply quantitative information concerning the rate of glucose utilization at different blood glucose (and insulin) concentrations. In this technique (Andres, 1968) the rate of glucose infusion is automatically adjusted to maintain a fixed glucose level, and the rate of infusion is then equal to the rate of glucose utilization at the selected blood glucose concentration.

Techniques are available for the study of the metabolism of relatively isolated tissues *in vivo*. The most frequently used is the isolated forearm preparation. Using this procedure predominantly muscle or adipose tissue metabolism can be studied according to the venous drainage which is collected (Andres, Cader, and Zierler, 1956).

Finally it may be possible to remove pieces of tissue in order to study their metabolism more specifically. One difficulty here is that the procedure of removal, often involving anaesthesia, disturbs metabolism, though this could be minimized by a deep-freeze technique. Another difficulty is that the rate of metabolism must be deduced from a single sample. If the tissue is incubated *in vitro* to measure the rate of reactions then the change in environment will eventually and possibly even very rapidly alter the behaviour of the tissue.

The demonstration of hyperinsulinaemia is frequently used as evidence of hyperinsulinism. Although this information is now fairly readily obtained it is in some ways the least informative of all the investigations, and certainly less valuable than the estimation of blood glucose. It is not uncommon for the question to be raised as to whether a patient suspected of having an insulin-secreting tumour should be surgically explored because of a certain plasma insulin concentration. In deciding on an exploration and possibly on a blind subtotal pancreatectomy the relationship of the symptoms and signs to the plasma glucose concentration and to the effect of oral glucose provide a much better guide than do plasma insulin concentrations.

It is a remarkable fact that there are relatively few good demonstrations of the relationship between hyperinsulinaemia and hyperinsulinism. The most that is done usually is to demonstrate the association of hyperinsulinaemia and hypoglycaemia. Whilst patients with insulin-secreting tumours often show this association it is not uncommon for the hyperinsulinaemia to be of lesser magnitude and duration than that seen in many cases of obesity. Nevertheless it remains true that hyperinsulinaemia is usually taken as an indication of hyperinsulinism and it is therefore worth considering the criteria of hyperinsulinaemia.

Hyperinsulinaemia may be defined with reference to the plasma insulin concentration in relation to a period of fasting or to a standardized procedure aimed at stimulating or indeed inhibiting (though this has yet to be used) insulin secretion. Alternatively in place of a single insulin concentration one may take an integrated estimation of several plasma insulin concentrations. There are three main procedures for doing this. (1) Estimation of the area under the curve formed by plotting plasma insulin levels at intervals after the administration of a stimulus (Perley and Kipnis, 1965); this area may or may not be corrected by subtracting the area under the projected fasting insulin concentration. (2) Summation of the plasma insulin concentrations measured at intervals after the administration of a stimulus; again the insulin concentrations may be calculated as increments over the basal (usually fasting) insulin concentration (Floyd, Fajans, Conn, Thiffaut, Knopf, and Guntsche, 1968). (3) Estimation of insulin output in urine; this depends on the assumption that a fixed proportion of the plasma insulin is recovered in the urine and therefore that changes in plasma insulin are reflected by proportionate changes in the urinary insulin output (Jørgensen, 1966; McArthur and Stimmler, 1966; Rubenstein, Lowy, Welborn, and Fraser, 1967). The above procedures may be considered as defining absolute hyperinsulinaemia.

Relative hyperinsulinaemia may be defined as either excessive rise in plasma insulin concentration

after the administration of a stimulus, considered in relation to the preceding insulin level (usually fasting), or as excessive rise in plasma insulin concentration considered in relation to the dose of stimulant given. It is of course also possible to measure the degree of relative hyperinsulinaemia by integrating the rise in plasma insulin level.

The value of these different indices lies mainly in their ability to provide a very indirect indication of two aspects of metabolism—insulin sensitivity and insulin secretory capacity.

If an individual after an overnight fast is considered to be in a steady state for a short period, then the fasting plasma insulin considered in relation to the plasma concentrations of the various parameters affected by insulin gives some sort of indication of the insulin sensitivity of the individual. For example, it seems reasonable to conclude that a person with high fasting plasma insulin and glucose concentrations is resistant to the hypoglycaemic action of endogenous insulin, without excluding the possibility that the insulin is abnormal in structure. Similarly, after displacing the fasting individual away from this steady state by administering a metabolic load one may attempt to estimate the amount of insulin which the pancreas must secrete in order to re-establish the original state. In this type of investigation it is assumed that an integrated estimate of plasma insulin concentration reliably reflects the amount of insulin secreted by the pancreas and made available to the tissues. In the determination of this type of index the insulin output over a fixed time is often used, but it seems more reasonable to estimate the insulin output up to the time at which the basal state is regained, even if the time period does not then remain constant.

Within the context of hyperinsulinism the investigation of the insulin secretory capacity of the individual is mainly important in relation to treatment. At the moment it appears that the most important cause of hyperinsulinism is oversecretion, and the treatment of hyperinsulinism due to oversecretion ought to be different from that due to an excessive action of a normal amount of insulin. If there is oversecretion it may occur in the presence of a normal stimulus to secretion or in the presence of an increased stimulus, and here again the treatment of the two types of oversecretion should differ. In practice, however, one may have to use the same treatment.

In relation to the insulin secretory capacity of an individual the most useful indices of hyperinsulinaemia are the relative indices. If one considers first the index relative to the fasting insulin concentration, any insulin output may reflect a relatively large output from a small number of β-cells or a relatively small output from a large number of cells. It is likely that the ability to produce a rise in plasma insulin concentration relative to the basal concentration will be much greater in the latter than in the former, because the secretory rate may already be near its maximum. Thus this index may give an indication of the basal strain on the insulin secretory mechanism as well as the reserve capacity of the system.

The index of plasma insulin concentration relative to the magnitude of the stimulus, the first such to be introduced, was the insulin/glucose ratio of Seltzer and Harris (1964), which gives an indication of the sensitivity of the secretory mechanism to that particular stimulus. On the basis of this index it may be possible to decide whether the β-cells are overstimulated or oversensitive. The sensitivity of the system is best tested by a sudden change in the concentration of stimulus followed by measurement of the early secretory response, for with time the response may improve, thereby decreasing the discrimination afforded (Hales, Greenwood, Mitchell, and Strauss, 1968).

In the future, attempts to assess hyperinsulinism by its effect on different tissues and different pathways may be improved by a careful consideration of the best parameters to measure. These should relate to as many as possible of the different metabolic pathways affected by the hormone, and should be relatively stable so that they do not alter significantly during the process of sampling. Determinations which might meet these requirements include intracellular potassium, glycogen, triglyceride, and the activities of enzymes known to be affected by insulin such as those of glucose phosphorylation and glycogen synthesis.

CLINICAL TYPES OF HYPERINSULINISM

EXOGENOUS HYPERINSULINISM This may occur when insulin is administered with therapeutic or suicidal intent. Anyone responsible for the care of diabetics is only too familiar with the hypoglycaemic effect of excessive insulin therapy. However, there may be more subtle signs of dysinsulinism during such treatment. Because of the route and timing of therapeutic insulin administration it is entirely possible that the effects of exogenous insulin on different tissues, especially the liver and the peripheral tissues (Steele, Bjerknes, Rathgeb, and Altszuler, 1968), and on different metabolic pathways in the tissues, may be quite different from those of endogenous insulin. To restrict our attention to one parameter of whole body metabolism, namely, blood glucose, is no longer adequate.

Suicidal or self-induced hyperinsulinism is relatively rare and because of this may be overlooked

The self-administration of insulin without suicidal intent has been reported on a number of occasions. It is of interest that some of these cases have come to light as a result of studies of insulin antibodies. Investigators have believed that they have discovered people with autoantibodies to insulin, only to find that these patients have been giving themselves insulin. In fact so rare are insulin antibodies in the absence of insulin treatment (Parker, Pildes, Chao, Cornblath, and Kipnis, 1968) that it is probably justifiable to regard their presence as good evidence for the previous administration of exogenous insulin, though this is not accepted by Penchev, Andrev, and Ditzov (1968).

Proof of the recent administration of exogenous insulin can be obtained, as illustrated by a case which we have studied. We were asked to estimate the plasma insulin concentration in a sample of blood taken from a nurse who died in hypoglycaemic coma. Due to the immunological properties of different species of insulin it was possible to estimate the total insulin in plasma and also to determine whether it differed from human insulin. To do this we used an antiserum which did not discriminate between human and ox insulin (Hales and Randle, 1963) to measure total insulin, and then one which discriminated between human and ox insulin[1]. Figure 1 shows the standard curves for human and ox insulin obtained using the latter antiserum. Figure 2 compares the effects of serial dilutions of samples of therapeutic ox insulin of plasma taken from the nurse with hypoglycaemic coma, and of human plasma taken after a glucose load (all containing approximately the same initial total insulin concentration) on the binding of labelled insulin by this antiserum. It may be seen that the dilution curves of the therapeutic ox insulin and of the sample from the nurse with hypoglycaemia are almost identical, whereas the curve of human plasma containing a high concentration of endogenous human insulin diverges widely.

[1]I am grateful to Dr B. A. L. Hurn of the Wellcome Research Laboratories, Beckenham, Kent, for the supply of this antiserum.

ENDOGENOUS RELATIVE HYPERINSULINISM All cases of hypoglycaemia, other than those due to absolute hyperinsulinism, may be considered as probable examples of relative hyperinsulinism as I have defined it. In order to determine whether such a situation exists one ought to inhibit insulin secretion and show that the abnormality is thereby corrected.

ENDOGENOUS ABSOLUTE HYPERINSULINISM This is most frequently found in subjects with an insulin-secreting tumour. It is characterized by hypoglycaemia combined with hyperinsulinaemia, and this state, which is variable in its occurrence, may be sought either in the fasting condition or following stimulation of insulin secretion by various stimuli (Marks and Rose, 1965).

Insulin-secreting tumours may be benign or malignant. Our experience has been that fasting plasma insulin levels in patients with benign tumours tend to be labile and may at their highest be only slightly above the normal fasting range. On the other hand the few cases of malignant tumours with metastases which we have seen show an approximately tenfold or greater elevation of the fasting insulin concentration, and this is much less labile. One of the most difficult problems in diagnosing any insulin-secreting tumour is the differentiation from obesity. People with insulin-secreting tumours find that they can allay their symptoms by a high carbohydrate intake and therefore frequently become obese. On the other hand hyperinsulinaemia is often present in obesity (see review by Hales, 1968)[2].

[2]See also contribution by Dr Taylor. ED.

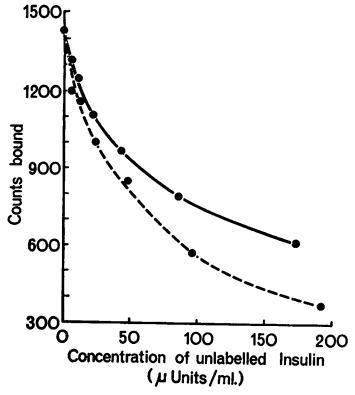

FIG. 1

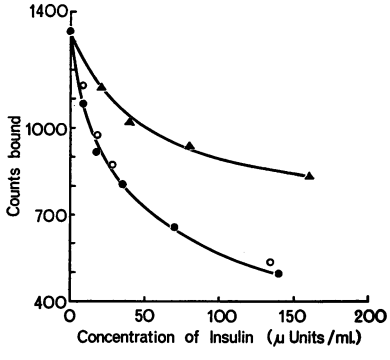

FIG. 2.

FIG. 1. *Standard curves showing the effects of human (——) and ox (— — —) insulins on the binding of labelled ox insulin by an antiserum to ox insulin.*

FIG. 2. *Effects of serial dilution of samples of therapeutic insulin (●), plasma taken from a subject in hypoglycaemic coma (○), and from a normal subject after a glucose load (▲) on the binding of labelled ox insulin by the antiserum used in the production of Figure 1.*

As a result of the work carried out by Rabinowitz and Zierler (1962), using the isolated forearm preparation, obesity is one of the few conditions for which a detailed documentation of hyperinsulinism is available. This work will be considered in some detail because it provides examples of the concepts of hyperinsulinism which I mentioned earlier. These authors studied obese subjects after an overnight fast, and by collecting deep venous and superficial venous blood from the isolated forearm attempted to study separately the metabolism of muscle and of skin plus subcutaneous adipose tissue. They found that the effect of obesity differed in the two tissues.

In the studies of blood draining muscle, fasted control subjects showed a net movement of potassium ions out of resting muscle into plasma, whereas there was no net movement of potassium ions seen in the obese subjects. Muscle glucose uptake was greater in obese subjects, but there was no difference in the lactate or CO_2 production or O_2 uptake of the two groups, the RQ being 0·7 in both. Rabinowitz and Zierler therefore concluded that the excess glucose uptake of the obese was accounted for by excessive deposition of glycogen. They found that the arterial-deep venous free fatty acid concentration difference was the same in the two groups.

In the studies of blood draining skin and subcutaneous adipose tissue they found no significant effect of obesity on potassium ions, glucose uptake, and lactate output. However, significantly less fatty acid appeared to be liberated by adipose tissue in the obese subjects.

Immunoassays of plasma insulin showed that the tissues of the obese subjects were exposed to higher insulin concentrations. It is therefore very interesting that although insulin stimulates glucose uptake by human adipose tissue and potassium uptake by rat adipose tissue, the hyperinsulinaemia of the obese did not affect these parameters in adipose tissue although in muscle it stimulated both. However, in adipose tissue a different parameter, namely, fatty acid release, was affected in a direction consistent with hyperinsulinism in the obese subjects.

The similarity of potassium movement and glucose uptake in the adipose tissue of both groups, despite the difference in plasma insulin levels, suggests the possibility that, even at the lower insulin levels found in the fasting controls, the response of adipose tissue is already approaching the maximum. Alternatively it is possible that the failure of adipose tissue to respond to the higher insulin levels found in obese subjects is due to the presence of an insulin antagonist. The latter possibility is supported by the results of raising the insulin level, which further increased glucose uptake in the controls but had less effect in the obese (potassium response was not reported). Higher insulin levels also inhibited fatty acid release from adipose tissue to a greater extent in the controls than in the obese subjects. If these effects are due to the presence of an insulin antagonist in the obese, it must be able to discriminate between the insulin effects of stimulating glucose uptake and of depressing fatty acid release in adipose tissue, because the former effect is the same in both groups whereas the latter is less in the obese subjects.

It is important to consider to what extent hyperinsulinism associated with normal or raised blood glucose levels occurs in other conditions. These include subjects on oral contraceptives (Javier, Gershberg, and Hulse, 1968; Spellacy, Carlson, Birk, and Schade, 1968); acromegaly (Beck, Schalch, Parker, Kipnis, and Daughaday, 1965), atherosclerosis (Peters and Hales, 1965; Nikkila, Miettinen, Vesenne, and Pelkonen, 1965); hypertriglyceridaemia (Davidson and Albrink, 1966), and diabetes mellitus (see review by Hales, 1968). However there is little or no information of the type outlined above which would allow one to reach a conclusion on this point.

TREATMENT OF HYPERINSULINISM

Before deciding the treatment one must decide whether the hyperinsulinism is pathological. In the case of benign insulin-secreting tumours neither decision is likely to be a problem, but in other conditions both may be particularly difficult. If it is accepted that the more subtle types of hyperinsulinism that I have defined can occur, then it is clear that morbidity and mortality from this type of imbalance may take a very long time to manifest themselves. An important reason for concerning ourselves with these considerations is the fact that drugs and hormones capable of inhibiting insulin secretion and action are now available: biguanides are capable of reducing the hyperinsulinaemia of obesity (Grodsky, Karan, Pavlatos, and Forsham, 1963); adrenaline and α-adrenergic drugs inhibit insulin secretion (Coore and Randle, 1964; Malaisse, Malaisse-Lagae, Wright, and Ashmore, 1967); diazoxide and other thiazide drugs will do the same (Seltzer and Allen, 1965; Howell and Taylor, 1966). These three groups of drugs act reversibly. The recently discovered antibiotic streptozotocin apparently acts irreversibly. An example of its use in treatment has been published (Murray-Lyon, Eddleston, Williams, Brown, Hogbin, Bennett, Edwards, and Taylor, 1968).

Hormones such as corticosteroids, growth hormone, and glucagon are capable of antagonizing some of the actions of insulin and have been used in the treatment of hypoglycaemia.

CONCLUSION

The aim of this paper has not been to review the literature but rather to indicate the problems which exist in relation to the investigation of the role of insulin in disease processes. A brief attempt has been made to suggest ways in which these problems may be attacked and to indicate some of the therapeutic possibilities which exist.

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